Immunosuppression in breast cancer: a closer look at regulatory T cells

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STELLINGEN BEHOREND BIJ HET PROEFSCHRIFT GETITELD:

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a closer look at regulatory T cells

Kevin Kos

1. Tumorigenesis enhances the immunosuppressive potential of T_{regs} in distant sites, thereby promoting metastasis development. *(This thesis)*
2. Therapeutic modulation of co-signalling engages both T_{regs} and conventional T cells, resulting in simultaneous activation of opposing pro- and anti-inflammatory effector mechanisms that can negatively impact immunotherapy response. *(Kumagai et al., Nat. Immunol. 2021; Kamada et al. PNAS, 2019; This thesis)*
3. Neo-adjuvant T_{reg}-inhibiting strategies in breast cancer patients may evoke anti-metastatic immune responses in axillary lymph nodes, thereby potentially limiting the development of lymph node metastasis. *(This thesis; Pul et al., J Immunother Cancer. 2019; Núñez et al., Nat. Comm. 2020)*
4. As the impact of T_{regs} on breast cancer progression is dependent on cancer subtype and immune composition, mouse models that closely mimic the diversity and the step-wise progression of human breast cancer subtypes are necessary to propel our understanding of T_{reg} biology to a higher level. *(This thesis)*
5. *In vitro* assays fail to reproduce the complex cellular and molecular interactions that exist *in vivo*, rendering these assays of limited value for studying metastatic niche-dependent processes. *(This thesis)*
6. Cancer-associated immunosuppression is a systemic, tissue-specific phenomenon, which impacts organotropism of metastasis. *(Spitzer et al., Nat. Med. 2020; this thesis)*
7. Complete understanding of the effect of immunomodulatory drugs on anti-tumor immunity requires a systems-based approach, as it cannot be fully unravelled by assessing single cellular components *(Garner & de Visser, Nat. Rev. Immunol. 2020; this thesis)*
8. Intratumoral immunosuppression consists of a multi-layered network. By dissecting separate layers, fundamental insights are gained that lay the foundation for the design of therapeutics which may, in the form of personalized combinations, dismantle cancer-associated immune suppression. *(Salvagno et al. Nat. Cell. Biol. 2019, this thesis)*
9. "I saw with regret, (and all scientists have shared this feeling) that whilst the number of accurate instruments was daily increasing, we were still ignorant" *(A. von Humboldt, Personal Narrative of Travels to the Equinoctial Regions of America, 1799-1804).* We are not limited by the abundance of data, but by the relevance of our questions.